Bioequivalence of Topical Products

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Q& A

How to Characterize Similarity?

- Q1: Qualitative Similarity
  - Same components
- Q2: Quantitative Similarity
  - Same amounts of the same components
- Q3: Structural Similarity
  - Same amounts of the same components arranged in the same way

How do you measure Q3?

What does Q3 similarity imply about bioequivalence?

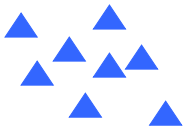
Definition of Q3

- Structural Similarity
  - Arrangement of matter
  - State of aggregation

Example: Polymorphs

Form A

Form B



Same Substance

Q3 is different

Example: Suspension

A

B

Same Substance

Q3 is different

What Determines Q3?

- Equilibrium states
  - Example: solution
  - Q2 implies Q3
- Non-equilibrium states
  - Examples: suspension, cream, ointment, gel
  - Determined by history
    - Manufacturing
    - Storage
    - Physical state of starting materials

How To Measure Q3?

- Different materials/formulations may require different methods
- General features
  - Particle/Droplet/Excipient size distribution
  - Spatial arrangement/homogeneity
  - Particle/Droplet/Excipient interactions or crosslinks or surface chemistry

Semi-Solid Dosage Forms

- Most topical products are semi-solids
  - In other fields semi-solids are referred to as complex fluids, soft condensed matter, or viscoelastic fluids
- Intermediate between liquid and solid
  - Depending on the measurement, their properties are a mixture of solid and liquid behavior

Phase Structure and Size Distribution

- Size distribution
  - Microscopy
  - Light scattering
- Phase structure/Spatial arrangement of particles
  - Differential Scanning Calorimetry (DSC) measurements

Interactions

- Interactions between the components of a semi-solid determine the rheology
  - Particle attraction or repulsion
    - Surface Charge
    - Excipients/Stabilizers
  - Polymer or gel crosslinking

Rheology of Semi-Solids

- Linear Viscoelasticity
  - Material response to oscillatory strain combines solid and liquid behavior
- Stress-Strain Rate Relation
  - Viscosity depends on strain rate
- Yield Stress
  - Stress required to induce flow

Drug Release From Formulation

- Diffusion Through Membrane
  - Franz Diffusion Apparatus: To determine the diffusional properties of drugs in various semi-solid formulations through biological membranes or artificial membranes

Relation of Q3 to Topical Product Performance

- For topical products rheology matters
  - Similar spreadability requires viscosity-shear rate curves and yield stress be the same
- Phase structure of formulation components
  - Manufacturing processes
- Drug release rate from formulation
  - How is the active ingredient contained in the formulation?

Regulatory Role of Q3

- Products that are Q1, Q2, and Q3 to each other will be bioequivalent?!

- Level of confidence in Q3 determination
  - Did we measure the appropriate property?
  - How similar must measurements be to be Q3?

Q3 Validation

- How to prove that Q3 determination is valid
  - Characterize complex formulations with particles of excipients and particles of actives
- University of Kentucky project
  - Measure rheology and drug release rates
  - Formulations with manufacturing differences
  - Formulation where generic was superior/(inferior), not equivalent, in a clinical trial

Topical BE: Q&A

- **DPK**
  - What type of studies should be conducted to validate the DPK method?
- **Q3**
  - What type of data is needed to demonstrate that two products are Q3 equivalent?
  - How should the Q3 concept be validated or demonstrated?
    - Demonstration that we can detect changes in manufacturing processes?
    - Demonstration that we can detect formulations with known differences?
    - Demonstration that drug release rates are identical?

Topical BE: Q&A

- **Bioequivalence for topical products**
  - What role should Q3 and DPK play in the demonstration of bioequivalence for topical products?
    - Under what circumstances should Q3 equivalence be sufficient to justify a wavier of in vivo bioequivalence tests?
    - Under what circumstances should Q3 equivalence and a DPK method in healthy subjects be sufficient to determine bioequivalence?